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(71) Applicant: IMPERIAL SENSUS, L.L.C. [US/US]; Suite 200, 8016 Highway 90–A, Sugar Land, TX 77478 (US).

(72) Inventors: ANFINSEN, Jon, R.; 6885 Stagge Road, Loveland, OH 45140 (US). ANFINSEN, Jonathan, S.; 9670 Murdoch Goshen road, Loveland, OH 45140 (US). TUNGLAND, Bryan, C.; 9375 Wood Crest Lane, Becker, MN 55308 (US).

(74) Agent: GOLDEN, Philip, T.; Locke Liddell & Sapp LLP, Suite 3400, 600 Travis, Houston, TX 77002–3095 (US).

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(54) Title: GRANULAR DELIVERY SYSTEM

(57) Abstract

There is disclosed delivery systems comprising granules and more specifically, granular compositions and methods of administering active ingredients in granular compositions. A composition comprises granules comprising an ingredient selected from the group consisting of carbohydrates, proteins and mixtures thereof. The average length of the longest axis of the granules is from about 0.75 to about 20 mm.

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# GRANULAR DELIVERY SYSTEM

**INVENTORS** Jon R. Anfinsen, Jonathan S. Anfinsen, and Bryan C. Tungland

## CROSS REFERENCE TO RELATED APPLICATION

Reference is made to and priority claimed from U.S. Provisional Application Serial No. 60/131,026 filed April 26, 1999, entitled "Granular Delivery System."

## TECHNICAL FIELD

This invention relates to delivery systems comprising granules. The invention further relates to granular compositions and methods of administering active ingredients in granular compositions.

## BACKGROUND ART

The major oral delivery system for drugs, nutritional supplements and dietary supplements are pills, tablets, capsules and liquids. Although these methods of delivery are common and usual, they can have serious disadvantages. Pills, tablets, and capsules are often difficult, and for some individuals perhaps impossible, to swallow. Difficulty in swallowing pills, capsules and tablets is a problem in a large percentage of the United States population. Such difficulties may cause gagging and, in severe cases, choking. Liquids, though often easier to swallow, tend to have problems related to palatability, ease of handling and degradation kinetics which often favor the rapid breakdown of active ingredients into forms that lack efficacy.

The disadvantage of pills, tablets, capsules and liquids are increased when multiple doses are to be ingested over a short period of time, for example, within a period of ten minutes, or when the ingestion must occur at frequent intervals within a day. When the ingestion of needed substances is difficult, compliance or adherence problems occur. Such non-compliance can ultimately be detrimental to a person's health and well-being.

The ingestion of common oral delivery systems often requires the swallowing of a relatively large dosage form or object, that is, a large pill or capsule, or a large volume of liquid. Swallowing such large dosage forms is especially difficult for children and elderly individuals, or for individuals whom have an impairment of swallowing.

One alternative to pills, tablets, capsules and liquids is the use of chewable tablets. Chewable tablets can provide advantages over pills, tablets and capsules in that as they are chewed they are more easily swallowed. However, chewable tablets often comprise drugs, nutritional supplements, dietary supplements or other biologically active materials which have unpleasant taste and which can be unpalatable. Providing palatable chewable tablets is not easily accomplished. Further, the mechanical abrasion resulting from chewing the tablets and the enzymes in the oral cavity can damage active substances or carriers that participate in product efficacy. Chewable tablets are often hard, and can present difficulties in chewing as well as cause tooth pain. Thus, chewable tablets generally have limited applicability.

The bio-availability of nutritional supplements and medications can vary based on body functions. For example, it is known that proper levels of stomach acid are needed in order to promote digestion in the stomach as well as facilitate the release of certain medications. It has been demonstrated that aging and disease conditions can severely reduce stomach acid and digestive enzymes, resulting in limited dissolution of the medication and thus reduce the bio-availability. The delivery of active substances to the blood stream requires that they be in a form or be converted to a form that can be readily absorbed and transported across the gastro-intestinal barrier. Proper functioning of the digestive system and the selection of the active ingredients helps achieve this goal. Unfortunately, antibiotics can kill beneficial intestinal bacteria that are required for good digestion. Oral dosage forms such as pills, tablets, capsules, chewable tablets and liquids typically do not enhance the bio-availability of active substances.

Additionally, it is not uncommon for individuals to experience adverse or unintended interruptions of normal body functions when certain medications are ingested. These adverse reactions include but are not limited to such disorders as diarrhea, constipation, nausea, abdominal pains, colitis, vaginitis, urinary tract infections and changes in blood sugar levels. For example, significant adverse reactions are often observed when antibiotics are administered. The antibiotics can kill important beneficial gastrointestinal bacteria which are necessary for digestion, support of the immune system, and maintenance of gastrointestinal health. Individuals weakened by disease, and the elderly, typically have a problem overcoming the interruption of normal body functions caused by the killing of beneficial intestinal bacteria.

Izuhara et al., U.S. Patent No. 4,868,180, disclose a vitamin-containing granule comprising vitamins and a binding agent, which may be pregelatinized starch, water-soluble cellulose, or a water-soluble high polymer such as dextrin, gun arabic, or gelatin. The granule size is such that the proportion of particles which do not pass the Japan Industrial Standard (JIS) 32-mesh sieve is not more than 5 weight percent and the proportion of particles which pass a JIS 145-mesh sieve is not more than 30 weight percent. As a 32-mesh sieve as defined the Japan Industrial Standard has a sieve opening size of 500$\mu$, thus not more than 5% of the particles of Izuhara et al. have a size of greater than 500$\mu$.

Giannani et al., U.S. Patent No. 4,966,770, disclose microencapsulated granules comprising prednisone and a dissolution promoter which have diameters of less than 1,000 microns. Dissolution promoters include polyethylene glycol, sucrose and lactose.

Kuhrts, U.S. Patent Nos. 5,461,511 and 5,466,469, discloses granular drug delivery systems having a gel-forming dietary fiber. The gel-forming dietary fiber includes plant gums, such as guar gum and locus bean gum, pectin or pectic substances, algal polysaccharides, glucomannan, cellulose, agar, lignin, and psyllium seed husks. The granules have a particle size of between about 30 and 100 mesh, U.S. standard.

Smits et al., U.S. Patent No. 5,656,317, disclose an agglomerated composition comprising at least one fructan exhibiting instant colloidal dispersion. The agglomerated composition is suitable for forming a creamy structure. The fructan may be inulin.

Green et al., U.S. Patent No. 5,792,754, disclose a nutritional composition suitable for enteral administration comprising dietary fiber which consists of soluble non-starch polysaccharides, such as gum arabic or pectin, insoluble non-starch polysaccharides, such as cellulose or hemi-cellulose, and algal saccharides, resistance starch and/or lignin. The algal saccharides may be inulin or hydrolyzed inulin. Green et al. teach that the composition may be in the form of a liquid or a powder.

There is a need for dietary supplements which can provide both dietary fiber and biologically active compounds in a palatable form.

There is also a need for methods of orally administering active compounds in compositions which are easily swallowed, may be consumed in large amounts, and which encourage compliance. There is a need for oral delivery systems which are conveniently administered to children and geriatric individuals, and for oral delivery systems which are conveniently administered to animals as well as humans. As used herein, "animals" refers to non-human mammals, fish, birds, reptiles and amphibians.

There is a need to provide compositions which can decrease the adverse effects of certain medications, and which will optimize bio-availability of active compounds.

There is further a need to provide for a composition which encourages proper functioning of the digestive system.

## SUMMARY OF THE INVENTION

It is an object of this invention to obviate the various problems of the prior art.

It is another object of this invention to provide delivery systems comprising granules.

It is an additional object of this invention to provide active ingredients in the form of easily consumable granules.

It is another object of this invention to provide a means of delivering active ingredients in forms which are palatable and easy to swallow.

It is yet another object of this invention to provide granules which contain active ingredients and may be easily ingested directly or which may be incorporated into foods or beverages.

It is yet another object of this invention to provide methods of regulating physiological responses. Such regulation of physiological responses include maintaining an acidic pH in the colon, optimizing absorption of drugs and/or nutrients, and promoting the growth of beneficial intestinal bacteria for promoting regularity of defecation.

It is yet another object of this invention to provide methods of nutritionally supplementing diet, administering health promoting active ingredients, providing active ingredients for treatment of diseases, and reducing adverse reactions in the administering of drugs.

In accordance with this invention, compositions are provided which comprise granules. The granules comprise a first ingredient selected from the group consisting of carbohydrates, proteins and mixtures thereof, wherein the average length of the longest axis of the granule is from about 0.75 to about 20 mm. The composition may comprise more than one type of granules. For example, the composition may comprise granules comprising carbohydrates and granules comprising proteins.

In accordance with a further aspect of the present invention, granules are provided comprising a first ingredient selected from the group consisting of carbohydrates, proteins, lipids and mixtures thereof, and a second ingredient selected from the group consisting of

active ingredients, enteric coatings, flavorings, colorings and mixtures thereof, with the proviso that the second ingredient is other than first ingredient.

In accordance with another aspect of the present invention, methods are provided for administering compositions to a human or animal, comprising orally administering compositions comprising granules. The granules comprise an ingredient selected from the group consisting of carbohydrates, proteins, lipids and mixtures thereof, wherein the average length of the longest axis of the granule is from about 0.75 to about 20 mm.

The foregoing has outlined rather broadly the features and technical advantages of the present invention so that the detailed description of the invention that follows may be better understood. Additional features and advantages of the invention will be described hereinafter which form the subject of the claims of the invention. It should be appreciated by those skilled in the art that the conception and the specific embodiment disclosed may be readily used as a basis for modifying or designing other compositions and methods for carrying out the same purposes of the present invention. It should also be realized by those skilled in the art that such equivalent compositions and methods do not depart from the spirit and scope of the invention as set forth in the appended claims.

## DETAILED DESCRIPTION OF THE INVENTION

As used herein, "active ingredient" is intended to refer to agents which effect or are involved in physiological processes of the body or organism hosted by the body, such as yeast, bacteria or viruses. Such physiological processes include, for example, immune processes of the immune system, regulation of serum cholesterol and triglyceride levels, regulation of blood pressure, metabolism of food, regulation of appetite, metabolism and regulation of hormones, regulation of enzyme activity, the regulation of gastrointestinal processes and control of infections.

As used herein, "active ingredients" is intended to include drugs, nutritional ingredients, dietary ingredients, vegetative bacteria, bacterial spores, and enzymes. As used herein, "dietary ingredients" refers to those ingredients defined by the Dietary Supplement Health and Education Act of 1994, 21 U.S.C. § 321(ff)(1), which defines dietary ingredients as (A) vitamins; (B) minerals; (C) herbs and other botanicals; (D) amino acids; (E) dietary substances for use by man to supplement the diet by increasing the total dietary intake; or (F) concentrates, metabolites, constituents, extracts or combinations of any ingredients described in (A), (B), (C), (D) or (E), and ingredients selected from proteins, carbohydrates, short-

chained fatty acids, and lipids. As used herein "proteins" is intended to include native proteins, modified proteins and predigested proteins, while "carbohydrates" is intended to include digestible carbohydrates and non-digestible carbohydrates, in both modified and native form. As used herein, "herbs and other botanicals" is intended to include plants, parts of plants, plant extracts, and compounds of plant sources generally referred to as phytochemicals, including phytonutrients.

Applicants have found that when active ingredients are incorporated into granules, compliance can be significantly improved. The granules may be ingested directly, or incorporated into foods or beverages prior to ingestion. The palatability of the granules may be enhanced by the addition of flavorings and masking agents, or by coating unpalatable ingredients prior to incorporation into the granules.

It has also been found that the bio-availability of active ingredients in granules may be enhanced by incorporating ingredients which improve digestion, provide an acidic colonic pH and provide substrates for the colon to help maintain healthy mucosal membranes which will optimize absorption and movement of nutrients or active ingredient across the gastro-intestinal barrier.

As used herein granules are considered to be small particles or pellets that have grainy or coarse nature. A granule may be contrasted to a powder in that a powder consists of small, fine particles that are not rough or grainy but rather have a soft or dusty characteristic. The granules of the present invention may comprise any shape, such as, for example, spherical or oval. Generally, the length of the longest axis of the granule is at least about 0.1, preferably at least about 0.75, more preferably at least about 1, mm, and no greater than about 25, preferably no greater than about 20, more preferably no greater than about 15, and even more preferably no greater than about 5, mm. In one embodiment, the length of the longest axis of the granule is from about 0.1 to about 5 mm, preferably from about 1 to about 5 mm, more preferably from 2 to about 5 mm, and most preferably from about 2 to about 3 mm. In yet another embodiment, the length of the longest axis of the granules is from about 0.75 to 20 mm. The granules may be water soluble or water insoluble.

As used herein, "granular composition" refers to compositions comprised partly or entirely by granules. The granular composition may be consumed as such, or the granules may be mixed with a beverage or sprinkled on or incorporated into food, preferable soft food. The granular composition may comprise granules all of which have the same formulation, or may comprise granules of differing formulation, that is, the granular composition may

comprise a single type of granules of a mixture of more than one type of granules. In one embodiment the composition comprises at least first granules comprising an ingredient selected from the group consisting of carbohydrates, proteins and mixtures thereof, and optionally, second granules. Preferably the second granules comprise active ingredients.

The granules may be produced by a variety of granulation processes. Active ingredients may be incorporated into the granules in any suitable manner. Suitable methods of incorporating actives include entrapment in crystals, entrapment in molten liquids that are cooled to produce solids which can be size reduced; coating or agglomerating smaller particles using fluidized-bed driers; and pan coating; agglomerating using spray driers; coating or agglomerating using blenders that incorporate steam and liquids followed drying; forming mixtures of smaller particles that may contain solid binders and liquids by utilizing low pressure extrusion; utilizing pelletizers to compress mixtures; utilizing compactors or presses that can press small particles into acceptable sized granules; and by coacervation techniques. Solids may be sized-reduced by any suitable form of grinding or breaking, and may passed over or through a screen or sieve to control granule size.

The granules may be used in a granular form. Alternatively, the granules may be dissolved, suspended, or dispersed in a liquid, gel, or solid.

The granules may comprise one or more ingredients. Granules containing a single ingredient preferably contain an ingredient with biological activity, such as fiber, preferably inulin, protein or pre-digested protein. In one preferred embodiment, the granule consists of a single ingredient selected from modified or unmodified inulin, guar gum or maltodextrin.

In another preferred embodiment the granules comprise one ingredient which is the primary or major ingredient present at a level greater than any other ingredient. Such an ingredient, often called a carrier, may be an active ingredient or inert ingredient. Preferably the primary ingredient is a carbohydrate, protein or lipid, more preferably a carbohydrate or a protein, even more preferably non-digestible carbohydrate. In yet another embodiment the granules may comprise equal amounts of at least two ingredients, that is, the granule may have more than one ingredient but not have a major ingredient. In addition to carbohydrates, proteins and lipids, the granules may comprise ingredients such as active ingredients, inert ingredients, flavorings, binders, colorings, wetting agents and enteric coatings.

In one embodiment, the composition comprises granules which comprise an ingredient selected from the group consisting of carbohydrates, proteins, lipids and mixtures thereof. The granules may comprise the ingredient at a level greater than any additional

ingredients, i.e., the granule may comprise a carrier selected from carbohydrates, proteins, lipids and mixtures thereof. Suitable carriers include natural proteins, modified natural proteins, natural carbohydrates including inulin and sucrose, modified natural carbohydrates such as modified inulin, and molecules comprising chains of fructose or chains of dextrose. In one embodiment the granules comprise from about 0.5 to about 100 percent, by weight of the granules, of a carrier, preferably a carrier selected from carbohydrates, proteins, lipids and mixtures thereof.

Suitable non-enzymatic proteins for use herein include soy proteins, which may be supplied by soy flour, soy concentrates, or soy isolates. The proteins may serve as inert substances which are used as a diluent or vehicle to deliver a biologically active substance, or the proteins may provide biological activity themselves.

As used herein, "carbohydrates" is intended to include natural and modified sugars, natural and modified starches, natural and modified celluloses, and natural and modified gums which may serve as sources of energy and fiber. The basic unit of carbohydrate has a general formula $C_6H_{12}O_6$. This basic unit is called a simple sugar or monosaccharide. Monosaccharides may be combined to produce chains of saccharide units, such as disaccharides, trisaccharides, tetrasaccharides, or higher polymers containing thousands of sugar units. As used herein, the term "oligosaccharide" is used to refer to carbohydrates containing from about 2 to about 10 saccharide units, while the term polysaccharides is used to refer to carbohydrates having more than 10 saccharide units. Complex carbohydrates such as starch and dietary fiber are considered to be oligosaccharides or polysaccharides depending on the number of saccharide units.

Suitable carbohydrates for use herein include monosaccharides such as fructose and dextrose; disaccharides such as sucrose, lactose, lactulose, and maltose; oligosaccharides; polysaccharides (inulin, pectin, gums, cellulose, maltodextrins); sugar alcohols, such as xylitol, mannitol, sorbitol, maltitol, lactitol; native and modified starches, and native and modified gums.

Disaccharides and polysaccharides are not absorbed into the blood stream from the small intestine unless they are first hydrolyzed to monosaccharides. Oligosaccharides and polysaccharides which are not hydrolyzed by enzymes in the small intestine pass through the small intestine into the large intestine. These carbohydrates which are not hydrolyzed in the small intestine are known as non-digestible carbohydrates. The non-digestible carbohydrates serve as dietary fiber, and although not hydrolyzed by the enzymes of the small intestines,

may be hydrolyzed and fermented by colonic microflora. As used herein, "dietary fiber" is a plant polysaccharide or lignin which is not hydrolyzed to saccharides by the human digestive system. Non-digestible carbohydrates suitable for use herein include inulin, guar gum or maltodextrin in both native and modified form. Suitable forms of modified carbohydrates include hydrolyzed, acid-modified, esterified, cross-linked, hydroxyalkylated and acetylated carbohydrates.

The fermentation of non-digestible carbohydrates can provide beneficial physiological effects. While not being bound by theory, these effects are believed to include increased stool weight resulting from the increased bacterial mass; increased stool frequency; reduced constipation; increased colonic population of beneficial bacteria such as bifidobacteria and lactobacillus; inhibition of colonic pathogens; enhancement of digestion and utilization of nutrients; decreased urinary excretion of nitrogen; reduction of serum cholesterol and triglycerides; improved glucose tolerance and insulin sensitivity; and improved utilization of estrogen in women.

A preferred non-digestible carbohydrate is inulin. As used herein, "inulin" refers to modified and native inulin. Inulin is a natural non-digestible carbohydrate that is produced within plant cells. It consists predominately of linear chain of 1,2-β-linked-fructrofuranose units bound by a (α1-β2) type linkage to a terminal glucose unit. Inulin can be an oligosaccharide or a polysaccharide, and yields fructose and glucose upon acid hydrolysis. Typical sources of inulin are plant sources such as chicory or Jerusalem artichoke. Inulin from chicory is a mixture of oligomers and polymers of fructose having varying degrees of polymerization (DP) but typically having DP from about 3 to about 60 with a modal chain length of about 9. Inulin can be classified as a medium chain length fructooligosaccharide (FOS). Other FOS can be synthesized enzymatically from sucrose. Pure inulin occurs in spherical crystals that have radial striations. Purified native inulin from chicory is white, amorphous, hygroscopic and has a molecular weight of about 1600. It is neutral in order and tastes slightly sweet.

Inulin passes through the oral cavity, stomach and small intestine relatively unaltered. Instead of being hyrolyzed into saccharides, inulin is fermented by bacteria in the large intestines into short chain fatty acids. As inulin is not hydrolyzed to saccharides, it is a preferred carbohydrate source for diabetics and is believed to improve carbohydrate and lipid metabolism in diabetics.

In one embodiment of the invention the granules comprise inulin. The inulin can serve as a carrier and/or a granulating aid. When employed in granules in an effective dose, inulin can compliment other active ingredients, improve bio-availability of ingredients, improve bodily functions, prevent diseases, reduce drug side effects and help to regulate bodily functions. As used here, "effective dose" refers to an amount of inulin sufficient to effect a physiological process of the body.

Beneficial intestinal bacteria, such as bifidobacteria and lactobacillus, utilize inulin for growth and proliferation. Both beneficial and potentially detrimental flora inhabit the lower gastrointestinal tracts, but many pathogenic and putrefactive bacteria cannot utilize inulin as a substrate for growth. Thus, the inulin provides a food source for the beneficial organisms but not the detrimental organisms.

Additionally, the growth of bifidobacterial and lactobacillus produces acids, particularly short chain fatty acids, which lower the intestinal pH. Lowering the colonic pH favors the production of beneficial bacteria while inhibiting the growth of harmful bacteria. Thus, fermentation of inulin results in a lowering of the colonic pH, which favors the production of beneficial bacteria, such as bifidobacteria and lactobacillus, while inhibiting the growth of harmful bacteria such as salmonella, shigella, listeria, camphylobacter, bacteroides, proteus, staphylococci, veillonellae, enterococci, streptococci spp., enteropathogenic E. Coli, Clostridium perfringens, Clostridium difficile and vibrio cholera.

The presence of inulin and its fermentation in the colon promotes health and well-being. While not being bound by theory, manners in which inulin is believed to promote health include:

improving digestion and nutrient absorption, particularly decreasing lactose intolerance and promoting the absorption of calcium;

eliminating toxins and carcinogen production;

inhibiting the growth of harmful bacteria;

increasing the production of small amounts of natural antibiotics which may help control undesirable bacteria in the colon;

lowering serum cholesterol and triglycerol levels;

maintaining normal blood glucose;

controlling diarrhea;

avoiding constipation;

producing vitamins $B_1$, $B_2$, $B_6$, $B_{12}$, niacin and folic acid by fermentation in the gut;

helping to eliminate irritable bowel syndrome;

providing immune stimulating compounds;

easing the effects of premenstrual syndrome (PMS);

reducing food intolerance;

promoting a healthy liver;

restoring normal intestinal bacterial during antibiotic therapy;

providing a guide to a source of fiber;

and helping to suppress appetite.

As used herein, "normal blood glucose" is intended to refer to blood glucose levels of from about 70 to about 120 mg/dl, or from about 3.9 to about 6.7 mmol/liter.

While not being bound by theory, inulin is believed to promote regularity of defecation and reduction of constipation as a result of acceleration of fecal transit time and an increase in fecal bulk and weight.

It is believed the minimum amount of inulin required to promote health is about 5 grams per day. However, to optimize the benefits of inulin, it is recommended that from 10 to 15 grams be taken daily. Such doses are typically too large to be conveniently taken by pill, tablet, chewable tablet or capsule. Inulin has limited stability in palatable liquids due to hydrolysis. Thus, a granular delivery system would provide the benefits of inulin while offering individuals a simple convenient delivery system that encourages compliance.

The granular composition may comprise from about 0.5 percent to about 100 percent, by weight of the composition, of a carbohydrate. Preferably the carbohydrate is selected from the group consisting of inulin, fructose molecules comprising chains of fructose, molecules made of chains of fructose terminated with a single sugar unit other than fructose, chains of fructose terminated with a non-sugar unit, sucrose and mixtures thereof. In a preferred embodiment, the composition comprises a non-digestible carbohydrate, preferably the non-digestible carbohydrate is selected from the group consisting of inulin, guar gum, psyllium fiber, fenugreek fiber, modified dextrins, grain fibers, legume fibers and mixtures thereof, more preferably the non-digestible carbohydrate is inulin. In yet another embodiment the granular composition comprises from about 4 to about 5 grams of inulin per 5 grams of granular composition.

The granular composition may comprise a first ingredient selected from the group consisting of carbohydrates, proteins, lipids and mixtures thereof, and may further comprise a second ingredient selected from the group consisting of active ingredients, enteric coatings,

flavorings, colorings, binders, wetting agents, and granulating aids and mixtures thereof. Suitable active ingredients include drugs, nutritional ingredients, dietary ingredients, vegetative bacteria, bacterial spores, and enzymes. Preferred enzymes include proteases, lipases, cellulases and amylases.

Vegetative bacteria, bacterial spores, enzymes, short-chain fatty acids and non-digestible carbohydrates are believed to improve bio-availability of other active ingredients. As used herein, "short-chain fatty acids" refers to acids having no more than about 4 carbon atoms. Preferred short-chain fatty acids include acetic acid, propionic acid, butyric acid and lactic acid. More preferably the short-chain fatty acid is butyric acid. Generally, the composition will comprise an amount of short-chain fatty acids sufficient to lower the colonic pH by from about 1 to about 2 pH units when consuming a 5 gram dose.

Preferred vegetative bacteria and bacterial spores are those of bifidobacteria and lactobacillus. Generally, the composition will comprise from about 250 million to about 1.5 billion, preferably about 1 billion, bacteria and/or bacteria spores per gram of composition.

The composition may comprise phytonutrients or other phytochemicals. "Phytochemicals" refer to all chemicals contained within plants, while "phytonutrients" refer to chemicals in plants which are believe to be important or necessary for maintaining health, supporting growth and extending life. The term "phytonutrients" has been recently popularized to refer in particular to plant chemicals which may affect health. While present in varying degrees in all plants, foods such as fruits, vegetables, grains, oils, nuts and seeds have greater contents of phytochemicals which serve as phytonutrients and which appear to promote good health. Good sources of phytonutrients include tomatoes, onions, garlic, green tea, grapes, black berries, broccoli, thyme, capsicum, parsley, ginger, carrots, rosemary, peppermint, cranberry, soybeans and blueberries.

There are also many health promoting phytonutrients found in plants that are not typically used for food. Examples of a few such plants include the pine tree (pine bark extract), echinacea, gingko biloba, valerian, kava kava, licorice, ginseng, black cohosh, aloe, billberry, cascara sagrada bark, don quai bark and nettle leaf.

Phytonutrients can be classified by the type of biological function which they provide or by the areas of the body in which they function. Such classifications include cardiovascular, dermatological, endrocrinological, gastrointestinal, hematological, immunological, neurological, respiratory, rheumatological and urological. Phytonutrients are believed to have numerous general functions such as anti-hypertension, anti-

inflammatory, anti-bacterial, anti-yeast, anti-pyritical, anti-oxidants, anti-parasitics, anti-viral, analgesic, anti-anxiety, anti-depression, anti-edemic, detoxifiers, diuretics, enzymes, immunomodulators, laxatives, and chemo-therapeutic agents.

Phytonutrients may also be classified by their basic chemical structure, and include terpenes, carotenoids, limonoids, phytosterols, phenols, flavanoids, anthrocyanidins, catechins and gallic acids, insoflavones, thiols, glucosinolates, allylic sulfides, indoles, isoprenoids, tocotrienols, tocopherols, lipoic acids and ubiquinones.

A single does of the granular composition is generally at least about 0.5 grams. In one embodiment a single does of the granular composition comprises from about 0.5 to about 2.0, preferably from about 1 to about 10, more preferably from about 2 to about 5, grams of the composition. The total daily dose of the granular composition is generally at least about 0.5 grams. In one embodiment the total daily dose of the granular composition comprises from about 0.5 to about 100, preferably from about 5 to about 50, more preferably from about 6 to about 15, grams of the composition. In another embodiment the daily dose is from about 0.5 to 50, preferably 0.5 to 15 grams of the composition.

The granular composition may be used to deliver active compounds, including vitamins, to animals or humans. When the granular composition is used as a system to deliver vitamins to humans, it is preferred that the composition be formulated to deliver the Referenced Daily Intake (RDI), of the vitamins. In one embodiment the granular composition comprises vitamins, including vitamins A, C, D, E, $B_6$, $B_{12}$ thiamin, riboflavin, niacinamide, folic acid, biotin and pantothenic acids. Preferably, the composition comprises vitamins considered to be anti-oxidant vitamins, that is, vitamins A, C and E.

A granular composition for use as a vitamin and mineral supplement may contain the essential nutrition required for humans, particularly for children. In addition to vitamins, the granular composition may comprise minerals such as calcium, iron, phosphorous, iodine, magnesium, zinc, and copper. The granular composition for use as a vitamin and mineral supplement may comprise phytochemicals, preferably phytonutrients, other than vitamins and minerals. The granular composition may comprise different types of granule, such as, for example, a first granule comprising vitamins and minerals, a second granule comprising phytochemicals and, optionally, a third granule comprising nondigestible fiber and/or protein. Alternatively, the granular composition may comprise one type of granule which comprises all the ingredients.

In a preferred embodiment a dose of the composition comprises the RDI of the vitamins, particularly of the anti-oxidant vitamins. The RDI for vitamin A is about 5,000 International Units (IU), the RDI for vitamin C is about 60 mg, and the RDI for vitamin E is about 30 IU. In one preferred embodiment the composition comprises, per 5 grams of composition, from about 4 to about 5 grams inulin, about 5,000 IU vitamin A, about 100 mg vitamin C, and about 30 IU vitamin E.

A gram of granular vitamin and mineral supplement may contain from about 0.5 to about 0.95, preferably from about 0.1 to about 0.9, grams more preferably 0.2 to about 0.8 of carbohydrate, preferably the non-digestible carbohydrate inulin; from about 10 to about 20,000, preferably from about 300 to about 5,000, IU vitamin A (supplies as ß-carotene); from about 10 to about 600, preferably from about 20 to about 200, mg vitamin C; from about 40 to about 4,000, preferably from about 125 to about 250, IU vitamin D; from about 5 to about 1,000, preferably from about 10 to about 200, IU vitamin E; from about 0.1 to about 20, preferably from about 0.5 to about 1.5, mg thiamine; from about 0.1 to about 20, preferably from about 0.5 to about 1.5, mg riboflavin; from about 0.1 to about 60, preferably from about 3 to about 60, mg pantothenic acid; from about 10 to about 500, preferably from about 30 to about 60, mg calcium; from about 2 to about 50, preferably from about 6 to about 12, mg iron; from about 10 to about 500, preferably from about 30 to about 90, mg phosphorous; from about 15 to about 1,000, preferably from about 150 to about 300, meq iodine; from about 10 to about 500, preferably from about 6 to about 30, mg magnesium; from about 6 to about 100, preferably from about 6 to about 30, mg zinc; and from about 0.1 to about 10, preferably from about 0.5 to about 1.0, mg. copper. Generally the daily dose of the granulated vitamin and mineral supplement will be about 3 grams for a child, and will be from about 4 to about 10 grams for an adult.

The granular composition may be used as a granulated anti-oxidant supplement comprising inulin, green tea extracts, grape seed extracts, vitamin C, vitamin A as betacarotene, vitamin E, and selenium. The green tea extract and grape seed extract provide phytonutrients that are anti-oxidants.

A gram of such a granulated anti-oxidant supplement will contain from about 0.5 to about 0.95, preferably from about 0.1 to about 0.9, grams inulin; from about 10 to about 300, preferably from about 50 to about 75, mg to green tea extract standardized to 60% polyphenols; from about 10 to about 300, preferably from about 50 to about 75 mg of grape seed extract standardized to 250 Porter Value Units (PVU); from about 100 to about 500,

preferably from about 40 to about 350, mg of vitamin C; from about 10 to about 20,000, preferably from about 300 to about 1,700, IU vitamin A supplied as betacarotene; from about 5 to about 1000, preferably from about 10 to about 200, IU vitamin E; and from about 2 to about 40, preferably from about 10 to about 20, mcg selenium. Generally the daily dose of the granulated anti-oxidant supplement will be about 5 to about 10 grams for an adult.

Suitable drugs for incorporation to the granular compositions include antibiotics, analgesics and cough suppressants. The drugs are incorporated such that a dose of the granular compositions, generally from about 5 to about 10 grams, comprises an effective amount of drug. As used here, "effective amount of a drug" refers to an amount of sufficient to provide the desired pharmacological process of the body.

Flavorings may be incorporated into the granules for increasing their palatability either when consumed directly, or in a beverage or in a solid food. In addition to increasing palatability, the granules may be flavored and colored to disguise their presence when added to foods.

Granulating aids may be used in the production of the granules. In addition to providing bulk for the granule, granulating aids may help form and bind the granule. Suitable granulating aids include sugars, starches, gums, proteins and syrups. Generally, the granulating aid is a sugar, starch, gum, or protein other than the carbohydrate or protein which is used as a major ingredient of the granule.

Liquids may be added to the granule formulation to enhance binding properties. Suitable liquids include water, wetting agents, glycols, acidic aqueous solutions, basic aqueous solutions, oils, neutral aqueous ionic solutions and alcohols. Such liquids serve as binders. In other embodiments of the invention, liquids may serve as the actives, as wetting agents, or as flavoring agents as well as serving as binders. Wetting agents accelerate dissolution of granules in water.

Components may be added to the granules which comprise the granular composition or control the point wherein within the stomach or lower gastrointestinal tract where the active ingredient is delivered and rate at which an active ingredient is delivered. For example, it may be desirable to deliver certain nutritional components or vegetative bacterial cells to the colon.

Enteric-coated granules provide a method of providing vegetative bacterial cells, bacterial spores, or labile nutritional components to the colon. Enteric coatings rely on the differences in the environment between the stomach and the intestines for their performance.

For example, the enteric coatings may comprise material which does not begin to dissolve until it comes in contact with the digestive enzymes or the pH of the small intestine. Suitable enteric coatings include cellulose acid phthalate, shellac, polyvinyl acetate phthalate, and hydroxypropyl methylcellulose phthalate. Individual ingredients used to formulate the granules and/or the granules themselves may be coated. Such coatings may also serve to mask the flavors of unpalatable ingredients.

The following Examples, while not limiting, serve to further describe the invention.

Example 1

Granules for use in a granulated vitamin-mineral supplement that contains essential nutrition for children are prepared by incorporating 830 mg of a commercial vitamin pre-mix into 3.17 grams of inulin. The vitamin-mineral granules contain 5,000 IU vitamin A, 60 mg vitamin C, 400 IU vitamin D, 30 IU vitamin E, 1.5 mg thiamin, 1.7 mg riboflavin, 20mg niacinamide, 2 mg vitamin B6, 400 mcg folic acid, 6 mcg vitamin B12, 40 mcg biotin, 10 mg panthothenic acid, 100 mg calcium, 18 mg iron, 100 mg phosphorus, 150 mcg iodine, 20 mg magnesium, 15 mg zinc, and 2 mg copper. A child would conveniently be provided the RDI for vitamins by consuming 4 grams of the vitamin-mineral granules.

The vitamin-mineral granules are prepared as follows:

a) Charge a 1000 liter fluidized bed mixer with 208 pounds of finely powdered (average length of the longest axis of the inulin is from about 0.5 to about 2.0 microns).

b) Turn on mixer and fluidize the bed.

c) Inject into the fluidized bed 25 pounds of water sprayed in a fine mist (2-3 minutes).

d) Mix for an additional 1 minute.

e) Discharge granules.

f) Sift to remove fines.

g) Package granules.

Example 2

Granules for use in a granulated anti-oxidant supplement that can be taken by adults and children are prepared. Each 5 grams of granules contains 4.5 grams of inulin, 100 mg of green tea extract standardized to 60 percent polyphenols, 50 mg of grape seed extract standardized to 250 Porter Value Units (PVU), 100 mg of vitamin C, 5,000 IU vitamin A supplied as B-carotine, 30 IU vitamin E, and 50 mcg selenium.

The anti-oxidant granules are prepared as follows:

a) Add to a fluidized blender, equipped with mills, 900 pounds of finely ground inulin powder and 100 pounds of antioxidant pre-mix.

b) Turn on mixer to fluidize the bed.

c) Turn on mills to grind together antioxidant pre-mix and inulin (2-3 minutes).

d) Inject into the fluidized bed 50 pounds of water sprayed in a fine mist (2-3 minutes).

e) Discharge mix into low pressure extruder/former that is equipped with a die that has 1.5 mm round holes.

f) Extrude the mixture at 80 psi while maintaining temperature at 60°C.

g) After granulation dry the granules to 3.0% moisture using a fluidizer drier and size in the range of 2-4 microns employing gentle sifting.

h) Package sized granules.

The granules provide a convenient method in which to deliver the Recommended Daily Values (RDV) of anti-oxidant vitamins as well as important phytonutrient antioxidants. Generally a child would consume from about 2 to about 3 grams of the vitamin granules, while an adult would consume from about 5 to about 10 grams.

Example 3

Granules for use in a granulated vitamin-mineral supplement that contains essential nutrition for adults over 50 years old is prepared by incorporating 900 mg of a commercial vitamin-mineral pre-mix into 4.10 grams of inulin. The vitamin-mineral granules contain 5,000 IU of vitamin A, 60 mg vitamin C, 400 IU vitamin D, 609 IU vitamin E, 1.5 mg of thiamin, 1.7 mg riboflavin, 20 mg niacinamide, 4 mg vitamin B6, 400 mcg folic acid, 30 mcg B12, 40 mcg biotin, 10 mg panthothenic acid, 200 mg calcium, 5 mg zinc, 2 mg copper, and 100 mg phosphorous. Five grams of the granules conveniently provides the RDI for adults over 50 years old. The vitamin-mineral granules are prepared as follows:

a) Charge a 1000 liter fluidized bed mixer with 180 pounds of powdered vitamin-mineral premix (diameter approximately 0.5 to 1.0 micron) and 820 pounds of finely ground inulin (diameter approximately 0.5 to 2.0 micron).

b) Turn on mixer and fluidize the bed.

c) Inject into the fluidized bed 50 pounds of water sprayed in a fine mist (approximately 2-3 minutes).

d) Mix for an additional 1 minute.

e) Discharge granules.

f) Sift to remove fines.

g) Package granules.

Example 4

Antioxidant granules containing the phytonutrient antioxidants, green tea extract and grape seed extract are prepared such that each gram of granules will contain 100 mg of green tea extract standardized to 80 percent polyphenol and 100 mg of grape seed extract standardized to 250 Porter Value Units (PVU). The antioxidant granules are prepared as follows:

a) Charge a 1000 liter fluidized bed mixer with 100 pounds each of powdered green tea extract and grape seed (approximately 0.5 to 1.0 micron diameter) and 800 pounds of finely ground inulin (approximately 0.5 to 2.0 micron diameter).

b) Turn on mixer and fluidize the bed.

c) Inject into the fluidized bed 25 pounds of water sprayed in a fine mist (approximately 2-3 minutes).

d) Mix for an additional 1 minute.

e) Discharge granules.

f) Sift to remove fines.

g) Package granules.

Example 5

A composition is prepared comprising the vitamin-mineral granules of Example 3 with the antioxidant granules of Example 4. Generally for an adult the granules would be mixed in a ratio of about 1 part antioxidant granules to about 5 parts of vitamin-mineral granules. Thus the composition would contain the RDI of the vitamin-minerals of Example 3 plus 100 mg each of green tea and grape seed extract when 6 grams of the mixture of granules is consumed. The granules may be dissolved in a liquid, such as orange juice, apple juice or water.

To further illustrate the versatility of the present invention, the following formulation examples are provided:

Notes on ingredients:

1. Powdered sugar without starch.

2. Inulin (Frutafit® Inulin IQ, Imperial Sensus, LLC).
3. Vitamin/mineral mix for chewable tablets from Fortitech per specification below.
4. Grape seed extract (ActVin™ Interhealth) natural flavonoids and carotenoids.
5. Green tea extract (Sunphenon 100S-std. to 70% polyphenols-catechin, kaempherol, quercetin, and myricetin).
6. Theanine (bitter masking agent for extracts).
7. Whey protein isolate (Isolac, Century Foods, Int'l/Norben Co.-90% min. protein).
8. Sucralose (high intensity sweetener, McNeil Specialty Products).

Formulations run using 2.0 mm-1.2 T die, 45 rpm unless stated otherwise.

## MINIMUM AMOUNTS OF VITAMINS AND MINERALS PER 830 MG OF VITAMIN/MINERAL PREMIX

| | | |
|---|---|---|
| Vitamin A (as Beta Carotene, FCC) & (Acetate, USP-FCC) | 500 | IU |
| Vitamin $D_3$ (as Cholecalciferol, USP-FCC) | 400 | IU |
| Vitamin E (as Acetate, USP-FCC) | 30 | IU |
| Biotin (FCC) | 40 | mcg |
| Folic Acid (USP-FCC) | 0.4 | mg |
| Niacinamide (USP-FCC) | 20 | mg |
| Pantothenic Acid (as D-Calcium Pantothenate, USP-FCC) | 10 | mg |
| Vitamin $B_1$ (as Thiamin Mononitrate, USP-FCC) | 1.5 | mg |
| Vitamin $B_{12}$ (as Cyanocobalamin, USP) | 6 | mcg |
| Vitamin $B_2$ (as Riboflavin, USP-FCC) | 1.7 | mg |
| Vitamin $B_6$ (as Pyridoxine HCI, USP-FCC) | 2 | mg |
| Vitamin C (as Ascorbic Acid, USP-FCC) | 60 | mg |
| Calcium (as Dicalcium Phosphate, FCC) | 100 | mg |
| Copper (as Cupric Oxide) | 2 | mg |
| Iodine (as Potassium Iodide, USP-FCC) | .15 | mg |
| Iron (as Ferrous Fumarate, USP-FCC) | 18 | mg |
| Magnesium (as Magnesium Oxide, USP) | 20 | mg |
| Phosphorous (as Dicalcium Phosphate, FCC) | 100 | mg |
| Zinc (as Zinc Oxide, USP) | 15 | mg |

**Process steps (low pressure/temperature extrusion):**

1. Inulin is weighed first and all water is added to the inulin
2. Mix in a low speed mixer using a paddle for approximately two minutes.
3. Sugar is weighed during the inulin/water mixing step and added immediately, preferably before two minutes to minimize inulin glass formation.
4. Weigh other ingredients and add to mixture during mixing.
5. Mix final mixture approximately 3 minutes prior to granulating in extrusion granulator.
6. Granulate using appropriate die, approximately 45 rpm and slow feed rate. Maintain motor amperage below 5.
7. Product is dried to a moisture level of approximately 5 percent and then screened through a 80 mesh sieve to remove fines.

**Process steps (fluid bed agglomeration):**

1. Components of the mixture are weighed and added to a fluid bed agglomerator.
2. Conditioned air is initiated to fluidize the particles
3. Atomized water is added slowly to build granules
4. Process is continued until granules are of appropriate size, as defined in patent
5. Granules are conditioned to remove excess surface moisture
6. Granules are screened to remove particles that are retained on a 20 mesh sieve and pass through a 80 mesh sieve.

**Formulation examples:**

A. Sugar/inulin based formulations

Sugar : Inulin Granules (Base carrier with inulin)

| | | % |
|---|---|---|
| Sugar | 144.0 g | 72.00 |
| Inulin | 50.0 g | 25.00 |
| Water | 6.0 g | 3.00 |
| Total | 200.0 g | 100.0 |

Vitamin Mix Nutrient Granule Formula

| | | %
|---|---|---|
| Sugar | 125.0 g | 62.50 |
| Inulin | 53.0 g | 26.50 |
| Vitamin Mix | 19.0 g | 9.50 |
| Water | 3.0 g | 1.50 |
| Total | 200.0 g | 100.0 |

(10 g ≈ 1 Tbsp & delivers 2.65 g inulin and 950 mg of vitamin mix.)

Chocolate Flavored Vitamin Mix Nutrient Formula

| | | %
|---|---|---|
| Sugar | 280.0 g | 56.00 |
| Inulin | 132.5 g | 26.50 |
| Vitamin Mix | 47.5 g | 9.50 |
| Cocoa flavor | 25.0 g | 5.00 |
| Water | 15.0 g | 3.00 |
| Total | 500.0 g | 100.0 |

(10 g ≈ 1 Tbsp & delivers 2.65 g inulin and 950 mg of vitamin mix.)

Citrus flavored Vitamin Mix Nutrient Formula

| | | %
|---|---|---|
| Sugar | 302.5 g | 60.48 |
| Inulin | 132.5 g | 26.49 |
| Vitamin Mix | 47.5 g | 9.50 |
| Water | 15.9 g | 3.18 |
| Lemon flavor | 0.5 g | 0.10 |

| | | |
|---|---|---|
| Orange flavor | 1.75 g | 0.35 |
| Total | 500.2 g | 100.0 |

(10 g ≈ 1 Tbsp & delivers 2.65 g inulin and 950 mg of vitamin mix.)

Unflavored Antioxidant Nutrient Formula

| | | % |
|---|---|---|
| Sugar | 344.85 g | 68.52 |
| Inulin | 132.50 g | 26.50 |
| Green tea ext | 3.75 g | 0.75 |
| Grape seed ext. | 3.75 g | 0.75 |
| Water | 15.00 g | 3.00 |
| Theanine | 0.15 g | 0.03 |
| Total | 500.00 g | 100.0 |

(10 g ≈ 1 Tbsp & delivers 2.65 g inulin and 750 mg of tea & seed ext.)

Citrus flavored Antioxidant Nutrient Formula

| | | % |
|---|---|---|
| Sugar | 342.6 g | 68.52 |
| Inulin | 132.5 g | 26.50 |
| Green tea ext | 3.75 g | 0.75 |
| Grape seed ext. | 3.75 g | 0.75 |
| Water | 15.0 g | 3.00 |
| Lemon flavor | 0.5 g | 0.10 |
| Orange flavor | 1.75 g | 0.35 |
| Theanine | 0.15 g | 0.03 |
| Total | 500.0 g | 100.0 |

(10 g ≈ 1 Tbsp & delivers 2.65 g inulin and 750 mg of tea & seed ext.)

Cream flavored Antioxidant Nutrient Formula

| | | %
|---|---|---|
| Sugar | 343.40 g | 68.67 |
| Inulin | 132.50 g | 26.50 |
| Green tea ext | 3.75 g | 0.75 |
| Grape seed ext. | 3.75 g | 0.75 |
| Water | 15.00 g | 3.00 |
| Cream flavoring | 1.50 g | 0.35 |
| Theanine | 0.15 g | 0.03 |
| Total | 500.05 g | 100.0 |

(10 g ≈ 1 Tbsp & delivers 2.65 g inulin and 750 mg of tea & seed ext.)

Cocoa/cream flavored: "nutrient mix"

| | | %
|---|---|---|
| Sugar | 304.6 g | 55.51 |
| Inulin | 132.5 g | 24.15 |
| Grape seed ext. | 3.75 g | 0.68 |
| Green tea ext. | 3.75 g | 0.68 |
| Water | 15.0 g | 2.73 |
| Cream flavoring | 1.5 g | 0.27 |
| Cocoa flavoring | 25.0 g | 4.56 |
| Vitamin Mix | 45.0 g | 8.20 |
| Whey protein isolate | 17.5 g | 3.19 |
| Theanine | 0.15 g | 0.03 |
| Total | 500.0 g | 100.0 |

(10 g ≈ 1 Tbsp & delivers 2.42 g inulin, 680 mg of green tea & grape seed ext., 820 mg vitamin mix, and 2871 mg whey protein).

B. Sugar Free Inulin-based formulations

Unflavored Antioxidant Nutrient Formula

| | | | |
|---|---|---|---|
| | | | % |
| | Inulin | 476.55 g | 95.31 |
| | Green tea ext | 3.75 g | 0.75 |
| | Grape seed ext. | 3.75 g | 0.75 |
| | Water | 15.00 g | 3.00 |
| | Sucralose | 0.80 g | 0.16 |
| | Theanine | 0.15 g | 0.03 |
| | Total | 500.00 g | 100.0 |

(10 g ≈ 1 Tbsp & delivers 2.65 g inulin and 750 mg of tea & seed ext.)

Unflavored Vitamin Mix Nutrient Granule Formula

| | | | |
|---|---|---|---|
| | | | % |
| | Inulin | 177.7 g | 88.85 |
| | Vitamin Mix | 19.0 g | 9.50 |
| | Sucralose | 0.3 g | 0.15 |
| | Water | 3.0 g | 1.50 |
| | Total | 200.0 g | 100.0 |

(10 g ≈ 1 Tbsp & delivers 2.65 g inulin and 950 mg of vitamin mix.)

Moreover, an effervescence-based granule delivery system may be created with various combinations of acid/base systems such as citric acid, fumaric acid, malic acid and the like, used in combination with sodium bicarbonate, potassium hydrogen carbonate and the like.

Having shown and described the preferred embodiment of the present invention, further adaptions of the compositions and methods described herein can be accomplished by appropriate modifications by one of ordinary skill in the art without departing from the scope of the present invention. The number of alternatives and modifications have been described herein, and others will be apparent to those skilled in the art. Accordingly, the scope of the present invention should be considered in terms of the following claims, and is understood not to be limited to the details of the compositions and methods described.

## CLAIMS OF THE INVENTION

What is claimed is:

1. A composition comprising at least first granules; wherein the first granules comprise an ingredient selected from the group consisting of carbohydrates, proteins and mixtures thereof, and further wherein the average length of the longest axis of the granules is from about 0.75 to about 20 mm.

2. A composition according to claim 1, wherein the ingredient is a carbohydrate selected from native nondigestible carbohydrates, modified nondigestible carbohydrates and mixtures thereof.

3. A composition according to claim 1, wherein the ingredient is a nondigestible carbohydrate selected from the group consisting of fibers from plant sources, bacterial sources and mixtures thereof.

4. A composition according to claim 3, wherein the ingredient is a nondigestible carbohydrate is selected from the group consisting of inulin, guar gum, psyllium fiber, fenugreek fiber, modified dextrins, grain fibers, legume fibers and mixtures thereof.

5. A composition according to claim 1, wherein the composition comprises, per 5 grams of composition, at least about 0.1 grams carbohydrate, and further comprises an ingredient selected from the group consisting of vitamins, minerals and mixtures thereof.

6. A composition according the claim 1, wherein the granules comprise a carbohydrate selected from the group consisting of native inulin, modified inulin and mixtures thereof.

7. A composition according to claim 1, further comprising a phytonutrient.

8. A composition according to claim 7, wherein the phytonutrient is selected from the group consisting of terpenes, carotenoids, limonoids, phytosterols, phenols, flavanoids, anthrocyanidins, catechins, gallic acids, isoflavones, thiols, glucosinolates, allylic sulfices, indoles, isoprenoids, tocotrienols, tocopherols, lipoic acids, ubiquinones and mixtures thereof.

9. A composition according to claim 1, further comprising second granules comprising an active ingredient.

10. A granule comprising a phytonutrient.

11. A granule according to claim 10, wherein the phytonutrient is selected from the group consisting of terpenes, carotenoids, limonoids, phytosterols, phenols, flavanoids, anthrocyanidins, catechins, gallic acids, isoflavones, thiols, glucosinolates, allylic sulfices, indoles, isoprenoids, tocotrienols, tocopherols, lipoic acids, ubiquinones and mixtures thereof.

12. A granule comprising:

(i) a first ingredient selected from the group consisting of carbohydrates, proteins, lipids and mixtures thereof, and

(ii) a second ingredient selected from active ingredients, enteric coatings, flavorings, colorings, binders, wetting agents and mixtures thereof with the provisio that the second ingredient is other than the first ingredient.

13. A granule according to claim 12, wherein the enteric coating is selected from the group consisting of cellulose acid phthalate, shellac, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and mixtures thereof.

14. A granule according to claim 12, wherein the average length of the longest axis of the granules is at least about 0.75 mm.

15. A granule according to claim 12, wherein the first ingredient is a nondigestible carbohydrate.

16. A granule according to claim 12, wherein second ingredient is an active ingredient selected from the group consisting of drugs, dietary ingredients, vegetative bacteria, bacterial spores, enzymes and mixtures thereof.

17. A granule according to claim 16, comprising bacteria selected from the group consisting of bifidiobacteria, lactobacillus and mixtures thereof.

18. A granule according to claim 16, comprising a dietary ingredient selected from the group consisting of vitamins, minerals, herbs and other botanicals, amino acids, proteins, nondigestible carbohydrates, insoluble fiber, short chain fatty acids and mixtures thereof.

19. A granule according to claim 18, comprising a short chain fatty acid selected from the group consisting of acetic acid, propionic acid, butyric acid, lactic acid and mixtures thereof.

20. A granule according to claim 12, further comprising a liquid selected from the group consisting of water, wetting agents, acidic aqueous solutions, basic aqueous solutions, oils, neutral aqueous ionic solutions, alcohols and mixtures thereof.

21. A method of administering a composition to an organism selected from the group consisting of humans and animals, comprising orally administering to the organism a composition comprising at least first granules, wherein the first granules comprise an ingredient selected from the group consisting of carbohydrates, proteins, lipids and mixtures thereof, wherein the average length of the longest axis of the granules is from about 0.75 to about 20 mm.

22. A method according to claim 21, wherein the ingredient is a nondigestible carbohydrate.

23. A method according to claim 21, comprising orally administering from about 0.5 to about 15 grams of the composition.

24. A method according to claim 21, wherein the composition comprises, per 5 grams of composition, at least 0.1 grams carbohydrate, and further comprises an ingredient selected from the group consisting of vitamins, minerals and mixtures thereof.

# INTERNATIONAL SEARCH REPORT

[redacted] onal Application No
[redacted] CT/US 00/11694

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A23L1/052

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | DATABASE WPI<br>Week 198318<br>Derwent Publications Ltd., London, GB;<br>AN 1983-43733k<br>XP002146816<br>& SU 938 900 A (AS KIRG. ORG. CHEM. ET AL.), 5 July 1982 (1982-07-05)<br>abstract | 1-8,<br>10-12,<br>14-16,<br>18,20 |
| Y | --- | 9,13 |
| Y | PATENT ABSTRACTS OF JAPAN<br>vol. 199, no. 74,<br>30 April 1997 (1997-04-30)<br>& JP 08 333243 A (NIPPON KAYAKU CO. LTD.),<br>17 December 1996 (1996-12-17)<br>abstract | 9 |
| | --- | |
| | -/--- | |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 11 September 2000 | 18/09/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Alvarez Alvarez, C |

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Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/11694

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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